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## **Case Report: Practicability of functionally based tractography of the optic radiation during presurgical epilepsy work up**

Schmitt, F C ; Kaufmann, J ; Hoffmann, M B ; Tempelmann, C ; Kluge, C ; Rampp, S ; Voges, J ;  
Heinze, H J ; Buentjen, L ; Grueschow, M

**Abstract:** Pre-operative tractography of the optic radiation (OR) has been advised to assess the risk for postoperative visual field deficit (VFD) in certain candidates for resective epilepsy surgery. Diffusion tensor imaging (DTI) tractography relies on a precise anatomical determination of start and target regions of interest (ROIs), such as the lateral geniculate nucleus (LGN) and the primary visual cortex (V1). The post-chiasmal visual pathway and V1 show considerable inter-individual variability, and in epilepsy patients parenchymatous lesions might further complicate this matter. A functionally based tractography (FBT) seems beneficial for precise OR identification. We assessed practicability of FBT for OR identification in a patient with occipital lobe epilepsy due to a temporo-occipital maldevelopmental tumor. The MRI protocol at 3 T included a T1-weighted sagittal 3D scan, a T2-weighted axial 2D scan and a DTI scan using an echo planar spin echo sequence. ROIs for fiber tracking of OR (LGN V1) were determined with T2\*-weighted fMRI-based retinotopic assessment. After DTI pre-processing and fiber tracking, paths with similar properties were combined in clusters for visual presentation and OR localization. Retinotopic phase maps allowed for the identification of V1 and LGN for a precise DTI-based reconstruction of OR, which was distant to the patient's tumor. Location and structure of ORs were comparable in each hemisphere. FBT could thus influence the human research of the extrastriate visual pathway and the risk management of post-operative VFD in epilepsy surgery.

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## **Case Report: Practicability of functionally based tractography of the optic radiation during presurgical epilepsy work up**

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## **Abstract**

Pre-operative tractography of the optic radiation (OR) has been advised to assess the risk for postoperative visual field deficit (VFD) in certain candidates for resective epilepsy surgery. Diffusion tensor imaging (DTI) tractography relies on a precise anatomical determination of start and target regions of interest (ROIs), such as the lateral geniculate nucleus (LGN) and the primary visual cortex (V1). The post-chiasmal visual pathway and V1 show considerable inter-individual variability, and in epilepsy patients parenchymatous lesions might further complicate this matter. A functionally based tractography (FBT) seems beneficial for precise OR identification. We assessed practicability of FBT for OR identification in a patient with occipital lobe epilepsy due to a temporo-occipital maldevelopmental tumor. The MRI protocol at 3 Tesla included a T1-weighted sagittal 3D scan, a T2-weighted axial 2D scan and a DTI scan using an echo planar spin echo sequence. ROIs for fiber tracking of OR (LGN & V1) were determined with T2\*-weighted fMRI-based retinotopic assessment. After DTI pre-processing and fiber tracking, paths with similar properties were combined in clusters for visual presentation and OR localization. Retinotopic phase maps allowed for the identification of V1 and LGN for a precise DTI-based reconstruction of OR, which was distant to the patient's tumor. Location and structure of ORs were comparable in each hemisphere. FBT could thus influence the human research of the extrastriate visual pathway and the risk management of post-operative VFD in epilepsy surgery.

## **Keywords:**

DTI; retinotopy; optic radiation; lateral geniculate nucleus; primary visual cortex, tractography

## **Introduction**

Partial visual field defects (VFD) are a well-known risk after anterior temporal lobe resection (aTLR) [1], and potentially curative surgery is sometimes avoided in occipital lobe epilepsy, because the risk for a subsequent impairing VFD is considered too high. Even small amounts of brain movement during aTLR can affect the surgeon's judgment of the correct localization of the OR. Recently a new workflow for optimizing this procedure-specific complication has been introduced [2]. In this context, pre-operative diffusion tensor imaging (DTI) tractography of the optical radiation (OR) has been advised in order to minimize the risk for VFD after resective epilepsy surgery [3,4]. In the light of new MRI-guided ablative surgery techniques [5], which are not hampered by perioperative brain movements, surgically relevant information may be obtained through the precise pre-operative visualization of functionally important anatomical structures.

Considerable inter-individual variability of the OR has been demonstrated in post mortem [6] and in vivo studies [7], but also non-invasively using MRI tractography [8]. MRI tractography traditionally relies on the precise anatomical determination of start and target regions of interest (ROIs), namely the lateral geniculate nucleus (LGN) and the primary visual cortex (V1). The post-processing method chosen can also greatly influence the tractography results [4]. We thus set out to minimize these inherent methodological difficulties through functionally based ROI determination. We report on a patient with pharmacoresistant occipital lobe epilepsy evaluated for resective epilepsy surgery and assessed for the practicability of a functionally based tractography (FBT) of the OR. The LGN and V1 were separately identified by fMRI-based retinotopic mapping [9,10] and subsequently used as ROIs for MRI tractography.

## **Material and Methods**

### **Case Presentation**

A 27-year-old, otherwise healthy female reported visual-autonomic auras with a feeling of discomfort, hyperventilation, tachycardia, and simple and unformed visual phenomena.

Seizure frequency varied between 0.5 and 4 seizures per month. The first seizure, at the age of 23, was a bilateral tonic-clonic seizure, preceded by a habitual visual-autonomic aura. MRI investigation revealed a cystic, partially contrast-enhanced lesion in the caudal part of the right medial and lateral occipito-temporal gyri, compatible with a maldevelopmental tumor (ganglioma or dysembryoplastic neuroepithelial tumor; see Figure 1). The patient took six sufficiently dosed antiepileptic drugs (AEDs) without achieving seizure freedom.

A presurgical evaluation was initiated, because she felt considerably distressed by her visual auras and their reoccurrence substantially limited the pursuit of her daily activities. During the video-EEG-monitoring a habitual aura with a rhythmical theta seizure pattern starting from the right temporo-occipital region was recorded (figure 1). Her maldevelopmental changes near the OR could be associated with anatomical variations, as already shown in patients with focal cortical dysplasia [11]. Therefore a functionally based tractography (FBT) of the geniculo-striate tract was performed. Visual acuity and visual fields as tested with automated static perimetry (Octopus 101 Perimeter; Haag-Streit, Koeniz, Switzerland) were normal.

### **MR-Data acquisition**

Data were acquired using a 3 Tesla Siemens MAGNETOM Trio scanner (Siemens, Erlangen, Germany) with an 8-channel phased-array head coil for signal reception and Syngo VA35 software. The MR protocol included a T1-weighted sagittal 3D scan (MPRAGE sequence, 192 slices, slice thickness: 1.0 mm, TE: 4.77 ms, TR: 2500 ms, TI: 1100 ms, flip angle: 7 degree, bandwidth: 140 Hz/pixel, scan time: 9:20 min), a T2-weighted axial 2D scan (TSE sequence, 72 slices, slice thickness: 2 mm, TE: 78 ms, TR: 3300 ms, acquisition matrix: 256 x 192, voxel size: 1.0 x 1.0 x 2.0 mm, scan time: 4:24 min) and a DTI-scan with a TRSE-EPI sequence [12]. The parameters of the DTI-scan were 68 axial slices with the same centre position of the image block as in the T2-weighted scan, TR: 8200 ms, TE: 89 ms, PAT-modus: GRAPPA (acceleration factor 3, 25% phase oversampling), slice thickness: 2.0 mm, acquisition matrix: 128 x 128, voxel size: 2.0 x 2.0 x 2.0 mm, 4 runs each with 2 averages and frequency adjustment for each run, total scan time: 4 x 4:39 min, each run with

one non-diffusion-weighted volume and 12 diffusion-weighted volumes (non-collinear diffusion gradient directions from Siemens MDDW mode), b-values of 1000 s/mm<sup>2</sup>. Furthermore a fMRI scan for retinotopic mapping with the following parameters: 38 slices parallel to the calcarine sulcus, acquisition matrix: 64 x 64, TE 30 ms, TR 2.4 s, 3.5 mm isotropic resolution, field of view 224 x 224 mm, a total of 5 runs with 112 volumes each, as specified below, was acquired.

### **DTI-Data pre-processing and fiber tracking**

The DTI images were co-registered based on the non-diffusion-weighted images of the first run using SPM5. Diffusion tensors were calculated for each voxel and further decomposed into eigenvalues and eigenvectors using the SPM diffusion toolbox [13]. On this basis, the apparent diffusion coefficient and flip angle maps were computed. The fiber tract reconstruction was carried out using a probabilistic approach [14] implemented in MATLAB version 7.9 (MathWorks, Natick, MA). Start and target ROIs for fiber tracking were determined by fMRI imaging (see below) and co-registered to the diffusion scans. The number of start voxels was 50 for the left and 40 for the right LGN, and 454 for the left and 369 for the right V1 area. The tractography analysis was performed independently with 1000 starts for each voxel in each ROI. Paths with similar properties (i.e., trajectories, length) were combined in clusters for visual presentation.

### **Retinotopic mapping**

The patient underwent T2\* MRI scanning of the occipital lobe at 3 Tesla (Trio, Siemens) during visual stimulation. Stimuli consisted of a phase reversing (6 reversals per second) circular checkerboard (radius: 8 deg radius; mean luminance: 4 cd/m<sup>2</sup>; contrast: 90%) that stepped through polar angles or eccentricities of the visual field in accordance with established retinotopic mapping techniques [9].

For this purpose the stimuli were projected (DLA-G150CL, JVC Ltd.) onto a screen using Presentation version 13.1 (NeuroBehavioral Systems). After a dummy stimulation period of

21 seconds, seven full 36 s cycles of the stimulus section stepping either through the polar angles as a rotating wedge for polar angle mapping (three repetitions) or through the eccentricities as an expanding ring for eccentricity mapping (two repetitions) were presented. A full retinotopic map comprising one polar angle and one eccentricity map took 10 min 06 s, such that the acquisitions with the repetitions acquired here took 22 min 45 s (5 scans, 273 s each). Retinotopic data were analysed using MrVista (MATLAB 2009b with Stanford VISTA-tools [15]). After registration of the T1 weighted images to the T2\* weighted images' coordinate frame the fMRI time series were projected onto the flattened representation [16,17]. Each voxel's time-series (TS) underwent the following analysis [9]: (1) Seven temporal samples were discarded to avoid transient onset artefacts; (2) TS were divided by the voxel's mean intensity; (3) TS were filtered with a high-pass cut-off of 4 cycles/scan; (4) TS of the two repetitions were averaged; (5) Fourier analysis was applied to the TS to obtain the amplitude and phase for each frequency; (6) the coherence with a sinusoid of a frequency equal to that of the visual stimulation (1/36 Hz) was calculated. The coherence and phase values in the flattened representation were blurred by convolving a Gaussian kernel (4 mm full width at half maximum) with the complex vector representation of the BOLD response. The blurred phase values that exceeded a coherence threshold that corresponded to  $p < 0.001$  [18] were then plotted on the flattened representation of the occipital lobe in pseudocolor.

## Results

LGN and V1 were clearly evident from the polar angle maps, as demonstrated by the sections through the anatomical images (Figure 2 A, B, and C) and the flat maps of the occipital lobe (Figure 3 D and G). The left and right LGN volume comprise 400 and 320 mm<sup>3</sup> respectively, which is within the 95% confidence interval of a previous quantitative fMRI-based LGN examination (mean  $\pm$  SD: 440  $\pm$  93 mm<sup>3</sup>; [19]). Further, in accordance with previous studies [19,20], the upper and lower contralateral hemifield is represented in the ventral and dorsal LGN portions respectively (Figure 3 A & B). These ROIs entered the FBT

to yield estimates of the OR in both hemispheres (Figure 4). On the affected hemisphere, the obtained OR reconstruction revealed a projection superior to the tumor. Importantly, the OR was found to be located at a distinct distance from the tumor. During the presurgical work-up further AED adjustment was successful in terms of reducing both frequency and severity of her habitual auras, so that resective surgery was deferred by the patient.

## **Discussion**

In the presented case the anatomical relationship of the tumor and the OR was scrutinized with the assistance of retinotopic mapping, such that FBT was a feasible supplement in the presurgical work-up of this patient.

Histologically, the cytoarchitecture of Brodmann's Area 17 (V1) is easily distinguishable from neighboring areas and a high degree of interindividual and even intraindividual (left vs. right hemisphere) variability has been reported [7,21]. Other eloquent cortical areas also display considerable intra- and inter-individual anatomical variability, as shown for certain motor areas, the somatosensory, the language and auditory areas [22]. In patients with focal epilepsy the determination of eloquent cortices can be further complicated by a commonly observed anatomical alteration of the eloquent cortex, which is driven by at least two interacting factors: (1) The epileptogenic lesion itself is identical with or forms a large part of the anatomical alteration. This has been observed in lesions which originate from an early disturbance in the individual's development, such as prenatal or infant cerebral insults [23,24], cortical malformations or developmental tumors [25,26]. (2) An anatomical alteration of the eloquent cortex was also observed in patients with epileptogenic lesions remote to the eloquent cortex [27], suggesting that the seizures, interictal cortical activity or other functional abnormality of the cortex lead to alteration of functional localization [28].

Taken together, the functional presentation of eloquent cortex can differ from interpolations derived from healthy individuals. Functional determination of eloquent areas has thus become a commonly used diagnostic tool in epilepsy surgery work-ups. fMRI studies are routinely used for language lateralization, and occasionally for memory and motor function



[29]. Here we demonstrate that fMRI-based retinotopic mapping combined with DTI (FBT) has a similar potential for the visualization of the OR. It should be noted that the use of retinotopic mapping allows for the simultaneous identification of LGN and primary visual cortex. In contrast, a simple block design stimulation approach with full-field or alternating hemifield visual stimulation would only assist the identification of the LGN, with additional scans required to delineate the primary visual cortex.

Magnetoencephalography (MEG) is a non-invasive, functionally based method, which is increasingly used to localize functional entities, such as language, motor and visual function [30]. MEG has also been used for retinotopical assessment of the human V1 region [31,32], offering an enhanced temporal resolution in comparison to fMRI. However, both studies mention problems concerning correct localization, and since MEG would fail to assess the localization of the LGN, MEG-based retinotopy will not become applicable to a clinical setting in the near future. Another alternative to fMRI-based identification approaches might be MRI-based anatomical identification approaches, such as proton density contrast imaging of the LGN [33,34].

Future studies are needed to address whether the specificity and sensitivity of these approaches are sufficient for a reliable presurgical work up. One inherent technical difficulty of all retinotopic methods is that of attention and fixation: even though performance of retinotopic mapping seems to be in part independent from attention [35], the individual needs to be able to fixate throughout the 25 minute examination time. It should be noted, however, that one to two polar angle mapping scans are sufficient for the ROI definitions of V1 and LGN. Thus omitting the eccentricity mapping scans would require the patient to fixate for only one to two scans, each lasting less than five minutes. Consequently, less than ten minutes of fMRI are sufficient for FBT. This method is still expected to be of limited practicability in young children and mentally or visually impaired patients. Our adult, unimpaired patient easily tolerated the fMRI procedure and expressed an interest in the potential benefits of functional data acquisition, both for her particular case as well as for the progress of epilepsy research in general. She was therefore not averse to undergoing additional MRI procedures.

## **Conclusions**

Detection of both ROIs, V1 and LGN, with a single, functionally based method, is feasible and circumvents possible anatomical errors caused by an undetermined anatomical alteration of functional cortex. The results of the presented FBT for OR determination need to be compared with anatomically based tractography, a method which has already been systematically assessed in patients after resective surgery both for temporal [3,4] and extra-temporal [4] lobe epilepsy. Based on our specific case reported here, FBT is a feasible procedure for preoperative visualisation of the OR and can be included with moderate time demands in routine clinical workflows. Only a large-scale post-operative analysis would confirm the potential benefit of FBT in comparison to the standard anatomical method.

This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans.

## **Conflicts of Interest and Source of Funding:**

All authors have no conflict of interest: neither the authors nor the author's institution have a financial or other relationship with other people or organizations that may have influenced the presented work.

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## Figure Captions

### Figure 1:

#### Structural MRI and patient EEG

**A:** T1-weighted MRI with contrast enhancement. **B:** corresponding T2-weighted MRI-images.

The green circles indicate the epileptogenic lesion with characteristic features of a dysembryoplastic neuroepithelial tumor. **C:** ictal EEG with rhythmic theta-activity seizure pattern (red rectangle, with maximum at electrodes T6 and O2) during a habitual visual-autonomic aura (note the tachycardia).

### Figure 2:

#### Retinotopic mapping of lateral geniculate nucleus

Polar angle representation for the lateral geniculate nucleus in sagittal, coronal, and axial view in A, B, and C, respectively in the right (left visual hemifield: reddish/yellow color code, arrow) and left hemisphere (right visual hemifield: bluish/green color code). The color key codes the visual field locations that correspond to the respective cortical visual field representations. It should be noted that in accordance with previous investigations, the upper and lower contralateral hemifield is represented in the ventral and dorsal LGN-portions respectively (panel A and B). Panel C depicts an axial slice through the dorsal portion of the left LGN, reflecting the lower hemifield (bluish color code), and the medial portion of the right LGN, reflecting the horizontal meridian (reddish color code).

### Figure 3:

#### Retinotopic mapping of visual cortex

Polar angle maps in the visual cortex. A, B, and C: Right V1 as defined from polar angle mapping rotating wedge stimulation in sagittal, coronal, and axial view. D,E: Polar angle maps are superimposed onto the flattened representations of the right (D) and left occipital lobe (E). The area boundaries of V1 (area 17 Brodmann), the second and third visual area (V2,

V3) dorsal (“d”) and ventral (“v”) meet at the foveal confluence at the occipital pole as indicated by “\*”. The color key codes the visual field locations that correspond to the respective cortical visual field representations. Note that there is an inverted representation of the left visual hemifield on the right hemisphere and vice versa. Anatomical directions: L - lateral, M - medial, D - dorsal, V - ventral.

**Figure 4:**

**Reconstruction of optical radiation, tumor and regions of interest**

Contralateral-posterior view angle of axial DTI-based reconstruction of the right (A) and the left hemisphere (B) and superior view angle of the right (C) and the left hemisphere (D). The optic radiation (OR) is colored red, the lateral geniculate nucleus violet, the V1 (area 17 Brodmann) pink and the tumor green. There is no contact between the fibers of the right OR (red) and the tumor (green). Also, the fibers of right OR have a similar appearance and distribution to those of the OR from the unaffected, healthy left hemisphere.